

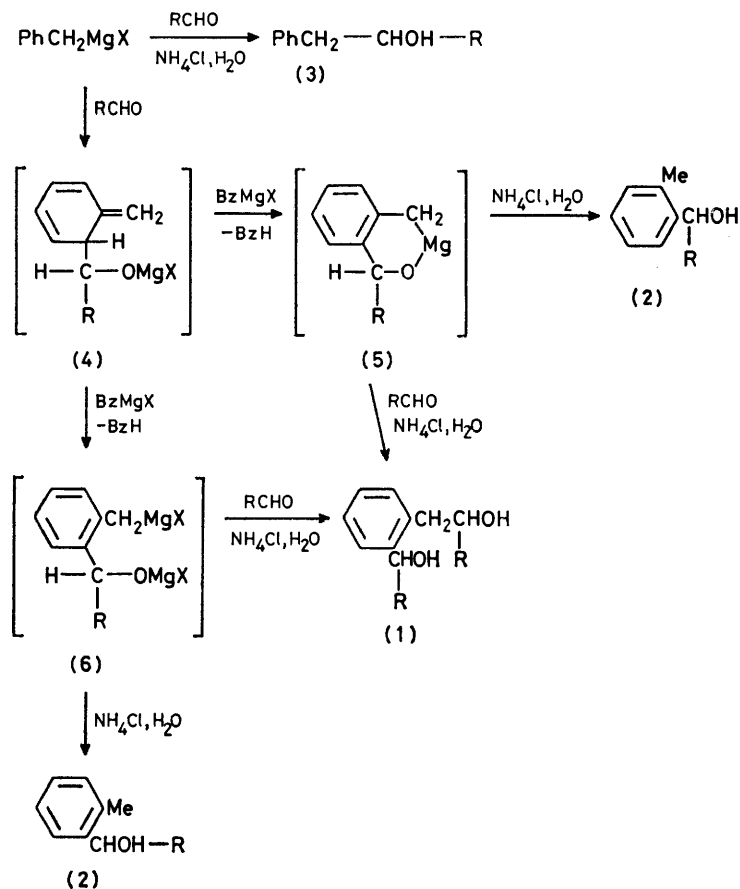
Mechanism of Diol Formation in the Reaction of Benzylic Grignard Reagents with Aldehydes

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2-Hydroxymethyl-1-methylene-1,2-dihydronaphthalene (8) was obtained from the reaction of 1-naphthylmethylmagnesium chloride with monomeric formaldehyde. This compound slowly produces approximately equimolar amounts of 1-methylnaphthalene and 1-(2-hydroxyethyl)-2-hydroxymethylnaphthalene (9) in the presence of $MgCl_2$. In the light of these results and studies on the reactivity of 1-naphthylmethylmagnesium chloride towards acetone and halide-free dibenzylmagnesium towards monomeric formaldehyde, a new mechanism of diol formation in the reaction of benzylmagnesium chloride with aldehydes is described. This mechanism involves an *ortho* addition on the Grignard reagent, leading to a trienic magnesium alkoxide intermediate (4), which decomposes by a reversible process into the Grignard reagent and aldehyde. The latter undergoes a Prins-type reaction with the magnesium alkoxide intermediate in the presence of $MgCl_2$, to give the corresponding diol and toluene.

As early as 1944, Young and Siegel¹ reported that the reaction of the benzyl Grignard reagent with citronellal led to the formation of an unexpected product which was assigned the structure of a diol. A similar result was

clearly established, as recently emphasized by Benkeser,⁸ and we now report the results of our studies which shed light on the pathway whereby diols arise from the reaction of benzylic Grignard reagents with aldehydes.



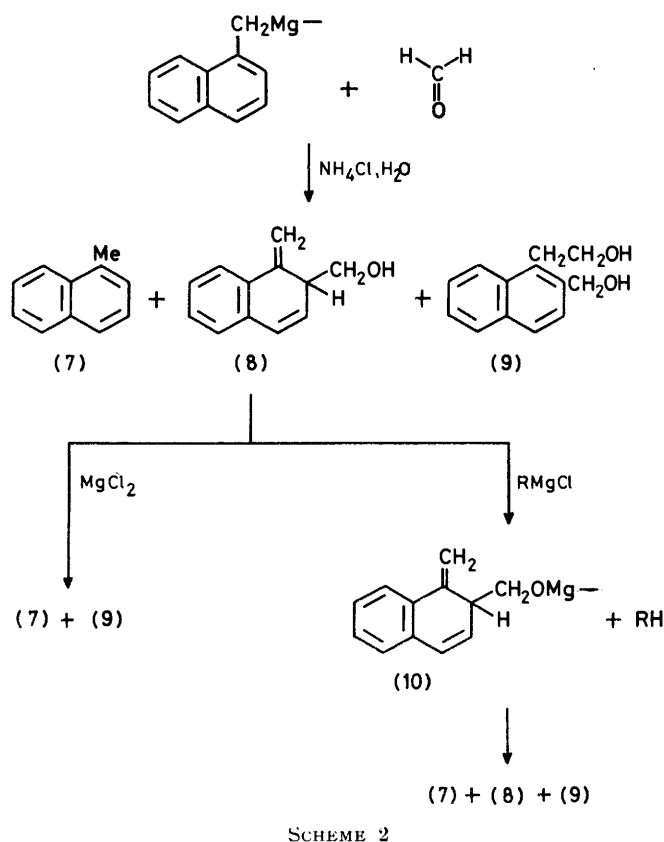
SCHEME 1

observed using benzaldehyde.² Furthermore, the diols (1) were found to be the main products of the reaction with unhindered aldehydes.³ Siegel, Nanomoto, and Benkeser¹⁻⁸ suggested the mechanism outlined in Scheme 1. However, this mechanism has never been

RESULTS AND DISCUSSION

Reaction of 1-Naphthylmethylmagnesium Chloride with Formaldehyde.—It has been reported⁹ that treating the Grignard reagent prepared from 1-chloromethylnaphthalene with gaseous formaldehyde produces 1-(2-

hydroxyethyl)naphthalene. We have found, on the contrary, that this reaction yields 1-methylnaphthalene (7) and a diol (9) (a result analogous to that observed with the benzyl Grignard reagent). More striking however was the fact that the major product isolated from the reaction mixture was 2-hydroxymethyl-1-methylene-1,2-dihydronaphthalene (8) (Scheme 2). This alcohol may be related to the trienic intermediate (4) postulated in Scheme 1, in order to account for the formation of the diol (1) and the alcohol (2). In addition, we have found that in the absence of formaldehyde and in the presence of $MgCl_2$, an ethereal solution of the pure alcohol (8) was converted into a mixture of 1-methylnaphthalene (7) and the diol (9) in the approximate ratio 1 : 1. These results suggest that the diol was not necessarily formed by reaction of an organometallic species with formaldehyde.

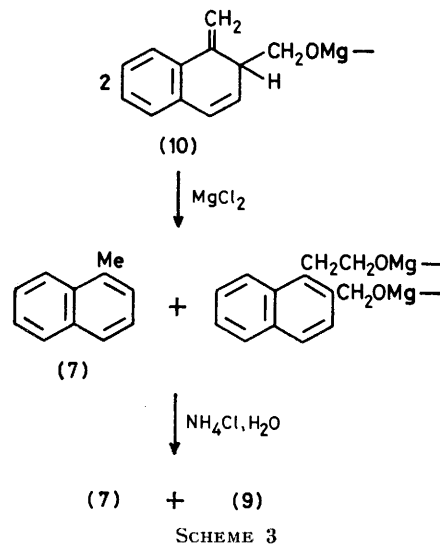


SCHEME 2

Similarly, allowing the reaction mixture to stand for four days at room temperature resulted in increasing yields of 1-methylnaphthalene (7) and the diol (9) at the expense of the alcohol (8) [it should be noted that the conversion of the alcohol (8) into 1-methylnaphthalene (7) and the diol (9) also occurred slowly]. Furthermore, the same evolution was observed from the magnesium alkoxide (10) prepared from the alcohol (8) (Scheme 2). These results strongly support the suggestion that the diol (9) arises from the alkoxide (10) rather than from intermediates like (5) or (6) (Scheme 1), as illustrated in Scheme 3.

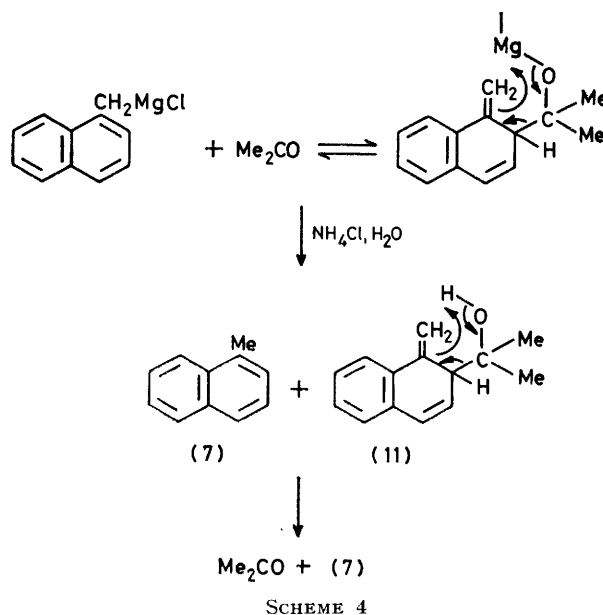
In order to further investigate the mechanism of diol

formation *via* an alkoxide intermediate, the Grignard reagent prepared from 1-chloromethylnaphthalene was allowed to react with acetone. Surprisingly, the pattern we observed for this reaction was very similar to that



SCHEME 3

observed for formaldehyde. Thus, an *ortho* reaction of the Grignard reagent occurred, resulting in formation of 2-(1-hydroxy-1-methylethyl)-1-methylene-1,2-dihydronaphthalene (11), which appeared to be of limited stability. N.m.r. data showed that allowing a sample of pure alcohol (11) to stand for four days at room temperature resulted in a 22% conversion into 1-methylnaphthalene and acetone (Scheme 4). Similarly, the yield of alcohol (11) was found to decrease as the amount



SCHEME 4

of 1-methylnaphthalene (7) increased when the reaction mixture was left for four days at room temperature instead of for 1 h at $0^\circ C$ before hydrolysis. According to these observations, the reaction of the Grignard re-

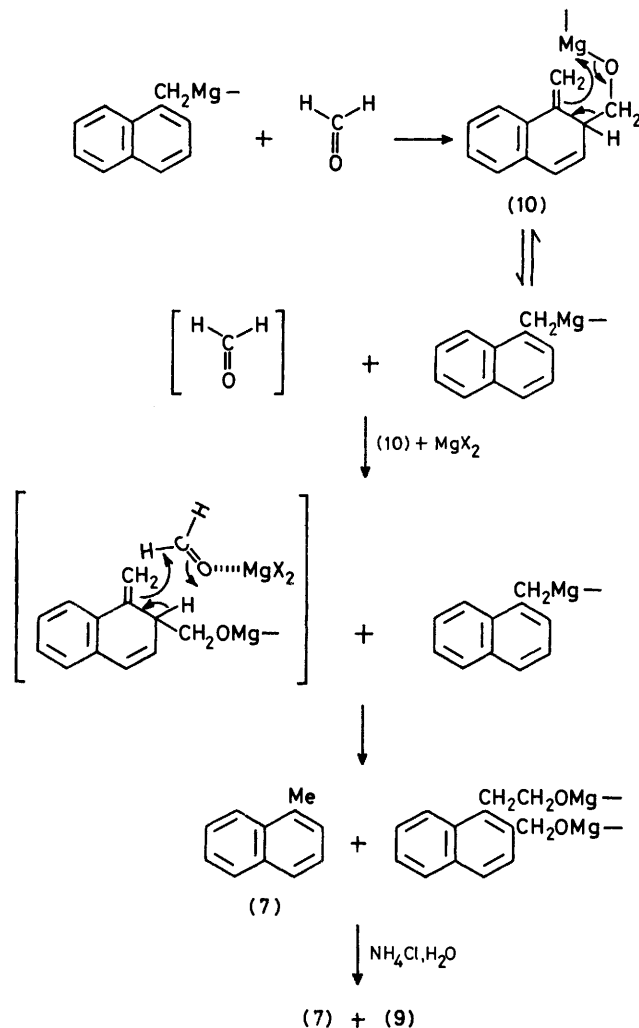
agent from 1-chloromethylnaphthalene with acetone can be viewed as occurring through a reversible *ortho* addition, as depicted in Scheme 4. Such a reversible addition of a $\beta\gamma$ unsaturated organometallic reagent on a ketone substrate could be predicted since it has been well established and documented in the case of the crotyl Grignard reagent.¹⁰ These observations support the suggestion that the reaction of the Grignard reagent from 1-chloromethylnaphthalene with formaldehyde would proceed similarly through an initial reversible *ortho* addition. On the other hand, methylenecyclohexane is known to undergo a Prins-type reaction with formaldehyde.¹¹ The Prins reaction also occurred with gaseous formaldehyde and 6-methylenecyclohexa-2,4-dienylmethoxymethane,⁵ a trienic intermediate very similar to that shown in Scheme 3. Therefore, the evidence gathered in this study is in best accordance with the mechanism outlined in Scheme 5 to account for the reaction of the Grignard reagent from 1-chloromethylnaphthalene with monomeric formaldehyde. Confirmatory evidence is brought by the following observations. First, the alcohol (8) is unstable, as already pointed out. Secondly, the decomposition of the alcohol (8) in the presence of $MgCl_2$, as well as of the alkoxide (10), always leads to a 1-methylnaphthalene-to-diol (9) ratio slightly greater than one. This may be explained by the fact that part of the formaldehyde arising from the reversal of alkoxide (10) escapes before diol formation can occur.

Mechanism of Diol Formation in the Reaction of Benzyl Grignard Reagent with Aldehydes.—In the light of the above results, we reinvestigated the reactivity of dibenzylmagnesium towards formaldehyde. It has been reported⁷ that the reaction of dibenzylmagnesium with aldehydes produces diol (1). We have found, on the contrary, that dibenzylmagnesium, obtained halide-free by precipitation of magnesium halides by dioxan and filtration, reacted with an excess of monomeric formaldehyde to yield the product distribution shown in the Table.

As will be noted, formation of the diol (1) from the alkoxide (4) (see Scheme 1) could be observed only in the presence of magnesium halides. This result closely parallels that forementioned in the case of the Grignard reagent from 1-methylnaphthalene (see Scheme 3). Therefore, it is reasonable to assume that diol formation in the reaction of the benzyl Grignard reagent with aldehydes proceeds through an *ortho*-alkoxide, according to Scheme 6.

Compared to the earlier suggestions (see Scheme 1), the mechanism we propose sheds some light on the interplay of variables operative in the reaction of the benzyl Grignard reagent with aldehydes. In particular, it rationalises in some degree the dependence of the product distribution on experimental conditions. Thus, when the Grignard reagent is made to react with an excess of aldehyde, the diol would arise *via* pathway B, but also by a direct Prins-type reaction of the *ortho*-alkoxide (4) with the aldehyde in excess, in the presence of magnesium

halides (pathway C). This accounts for the high yields of the diol (1) and the disappearance of the *ortho*-alcohol (2) observed in this case. Likewise, the high normal alcohol-to-diol ratio obtained when an excess of Grignard



SCHEME 5

reagent is used can be rationalised. The *ortho*-alkoxide not only would decompose to the diol (which in this case can only be formed by pathway B) but also to the normal alcohol by pathway A.

In summary, the results obtained in this study of the reactivity of the Grignard reagent from 1-chloromethyl-

Products from reactions of benzylmagnesium chloride
and dibenzylmagnesium with formaldehyde

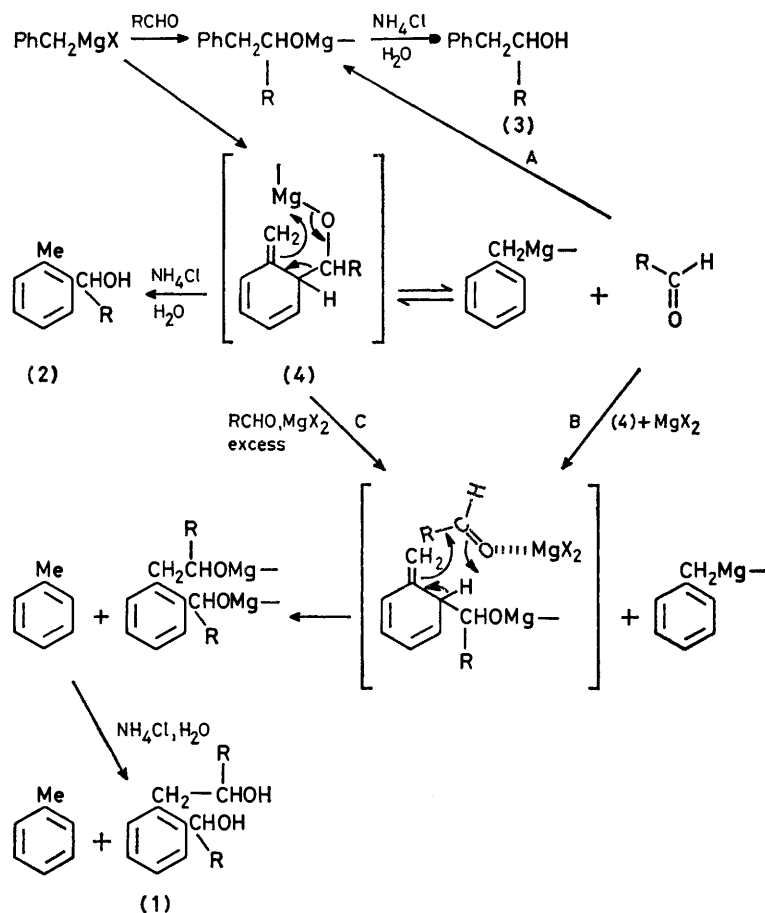
Product	PhCH ₂ MgCl	(PhCH ₂) ₂ Mg
2-Phenylethanol (12)	2.5	1.3
2-Methylbenzyl alcohol (13)	0.5	20
2-(2-Hydroxyethyl)benzyl alcohol (14)	20.5	Traces

naphthalene with monomeric formaldehyde and acetone show the behaviour of benzylic Grignard reagents to parallel that of allylic and particularly crotylic¹⁰ Grignard reagents.

EXPERIMENTAL

^1H N.m.r. spectra were recorded at 90 MHz on a Perkin-Elmer R 32 spectrometer (CDCl_3 solvent with tetramethylsilane as internal standard). ^{13}C N.m.r. spectra were recorded on a Bruker WH 60 instrument at 15.08 MHz. I.r. spectra were recorded on a Beckmann Acculab T.M. 10 spectrophotometer with CCl_4 as solvent. Mass spectra were obtained at 15 or 50 eV with an Atlas Mat CH_4 spectro-

stirrer, and a reflux condenser were added magnesium turnings (1.2 g, 0.05 mol). A small quantity of a solution of 1-chloromethylnaphthalene (7.06 g, 0.04 mol) in anhydrous diethyl ether (50 ml) was added to initiate the reaction. As soon as the reaction started, the flask was immersed in an ice-bath and the remaining 1-chloromethylnaphthalene solution was added dropwise over 1 h and the mixture was allowed to stir for an additional 0.5 h. The yield of Grig-



SCHEME 6

meter (probe temperature 110°C). All preparations and reactions involving air- and moisture-sensitive organometallic intermediates were conducted under an atmosphere of argon. All solvents were dried and purified according to standard procedures. Magnesium turnings (Merck) used for the preparation of organomagnesium reagents were of 99.5% purity. Standard titrimetric procedures were used for the estimation of organomagnesium concentrations. Hydrolyses were conducted by the slow addition at 0°C of 20% aqueous ammonium chloride and the organic product was extracted with diethyl ether. Anhydrous sodium sulphate was used as a drying agent for solutions in organic solvents. Column chromatography was performed using silica gel 60 (70–230 mesh ASTM) (Merck). G.l.c. was performed on 17% Carbowax 20 M at 170°C . M.p.s were determined with a Kofler apparatus.

1-Naphthylmethylmagnesium Chloride.—To a 0.5 l two-necked flask fitted with a dropping funnel, a magnetic

nard reagent by this method was over 95% (as determined by titration).

Formaldehyde.—Monomeric gaseous formaldehyde was prepared from paraformaldehyde as described by Benkeser *et al.*⁸ It was allowed to vaporise at room temperature in a stream of argon into the reaction vessel containing the Grignard reagent.

Reaction of 1-Naphthylmethylmagnesium Chloride with Formaldehyde. General Procedure.—To a flask containing the above Grignard solution was connected, *via* an addition tube, a test tube containing liquid formaldehyde prepared from paraformaldehyde (12 g). The liquid formaldehyde was allowed to vaporise at room temperature and the vapours were introduced above the stirred Grignard solution to avoid plugging of the addition tube. Addition was complete after *ca.* 0.5 h, whereupon the solution was stirred for 1 h at 0°C . The mixture was hydrolysed and then filtered. The residue and the aqueous layer were

extracted with diethyl ether, the combined ether extracts were dried, and then the ether was removed under reduced pressure at room temperature to afford a pale yellow liquid (6 g), a portion of which (1.2 g) was chromatographed on silica gel (50 g) with acetone-chloroform (3:22 v/v) as eluant. The following fractions were obtained: 1-methylnaphthalene (7) (0.35 g, 31%) as a liquid, δ 7.5 (m, 7 H, aromatic), 2.6 (s, 3 H, Me); 2-hydroxymethyl-1-methylene-1,2-dihydronaphthalene (8) (0.74 g, 54%) as a pale yellow oil, δ 2.2 (s, 1 H, OH), 3.4 (m, 2 H, $-\text{CHCH}_2-$), 5.1 (s, 1 H, methylene), 5.6 (s, 1 H, methylene), 5.97 (q, 1 H, J 0.5 Hz, =CH), 6.47 (d, 1 H, J 9.5 Hz, =CH), 7.15 (m, 3 H, aromatic), and 7.52 (m, 1 H, aromatic), ν_{max} 890 and 3 027 (methylene) and 3 450 and 3 500 cm^{-1} (OH), m/e 142 (M^+) (no molecular ion but allylic cleavage), δ_{C} 46.318 (d, C-2), 64.531 (t, = CH_2), and 114.496 p.p.m. (t, CH_2OH); and 1-(2-hydroxyethyl)-2-hydroxymethyl-naphthalene (9) (0.18 g, 11%), m.p. 121 °C (from ethanol), δ 7.9 (s, 1 H, OH), 3.4 (t, 2 H, $\text{CH}_2\text{CH}_2\text{OH}$), 3.9 (t, 2 H, $\text{CH}_2\text{CH}_2\text{OH}$), 4.4 (s, 1 H, OH), 4.85 (s, 2 H, CH_2OH), and 7.65 (m, 6 H, aromatic), ν_{max} 3 100 cm^{-1} (OH) (Found: C, 76.7; H, 6.85. $\text{C}_{13}\text{H}_{14}\text{O}_2$ requires C, 77.23; H, 6.93%). After standing for 4 days at room temperature the yields were: (7) 45%, (8) 12%, and (9) 33%. Decomposition of the alcohol (8) occurs slowly at room temperature to give small amounts of (7) and (9) and other unidentified products. Instantaneous decomposition occurs at temperature over 45 °C.

Reaction of the Alcohol (8) in the Presence of Magnesium Chloride.—To a solution containing the alcohol (8) (0.937 g, 0.0055 mol) in anhydrous diethyl ether (10 ml) was added magnesium chloride¹² (1.678 g, 0.0176 mol). The mixture was stirred for 4 days at room temperature, and then the reaction was quenched by addition of water. The precipitated white solid was dissolved in diethyl ether and the aqueous layer was extracted with diethyl ether. The combined ether extracts were dried and the ether was removed *in vacuo* at room temperature. The precipitated white solid was collected by filtration, washed several times with pentane, and dried to give the diol (9) (0.459 g, 42%), m.p. 120 °C, identical (^1H n.m.r. and i.r. spectra) with the sample obtained previously. Evaporation of the pentane solution gave a liquid (0.433 g, 56%), the ^1H n.m.r. and i.r. spectra of which were consistent with the structure of 1-methylnaphthalene (7).

Transformation of the Alkoxide (10).—To a solution of 1-naphthylmethylmagnesium chloride (0.01 mol) in anhydrous diethyl ether (20 ml) was added slowly at -70 °C the alcohol (8) (1.7 g, 0.01 mol) in anhydrous diethyl ether (10 ml). The mixture was allowed to stand for 4 days at room temperature before hydrolysis, and was worked up as in the general procedure to give 1-methylnaphthalene (7) (23%), the alcohol (8) (34%), and the diol (9) (18%). Similar results were obtained using benzylmagnesium chloride as the Grignard reagent.

Reaction of 1-Naphthylmethylmagnesium Chloride with Acetone. General Procedure.—To a solution containing the Grignard reagent (0.0182 mol) in diethyl ether (40 ml) was added slowly acetone (0.0182 mol) in diethyl ether (10 ml) at 0 °C over 15 min. The mixture was stirred for 1 h at 0 °C then hydrolysed and worked up as described previously to give 3.6 g of crude product. Column chromatography using acetone-chloroform (6:94 v/v) as eluant gave the following fractions: 1-methylnaphthalene (7) (0.184 g, 23%) and 2-(1-hydroxy-1-methylethyl)-1-methylene-1,2-dihydronaphthalene (11) (0.815 g, 73%), ν_{max} 3 565 and

3 470 (OH) 3 027 and 890 (methylene), and 2 970 cm^{-1} (methyl), δ 0.95 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 2.08 (s, 1 H, OH), 3.03 (d, 1 H, $-\text{C}-\text{H}$), 5.05 (s, 1 H, methylene), 5.64 (s, 1 H, methylene), 6.03 (q, 1 H, J 10 Hz, =CH), 6.52 (d, 1 H, J 10 Hz, =CH), and 7.25 (m, 4 H, aromatic) {all the ^1H n.m.r. spectra showed signals due to acetone [δ 2.03 (s, CH_3)] and 1-methylnaphthalene (7) [δ 2.62 (s, CH_3)]}; after column chromatography the ^1H n.m.r. spectrum showed a ratio of (7) to (11) of 1:4; after 4 days at room temperature the ratio was 11:15; δ_{C} 25.554 and 26.708 (q, $2 \times \text{Me}$) 54.453 (d, C-2), 73.334 (s, CMe_2), and 117.532 p.p.m. (t, methylene). After 4 days at room temperature before hydrolysis yields were 1-methylnaphthalene (7) 37% and the alcohol (11) 54%.

Dibenzylmagnesium.—To a 1 l three-necked flask fitted with a dropping funnel, a reflux condenser, and a mechanical stirrer were added magnesium turnings (21 g, 0.875 g-atom). To initiate the reaction a few ml of a solution of benzyl chloride (31.6 g, 0.252 mol) in anhydrous diethyl ether (550 ml) were added. As soon as the reaction started, the flask was immersed in an ice-bath and the remaining benzyl chloride solution was added over 4 h. When the addition was complete, the mixture was allowed to warm to room temperature and stir for an additional 1 h. To this solution was added slowly with vigorous stirring freshly distilled (over CaH_2) 1,4-dioxan (24.4 g, 0.277 mol). After vigorous stirring for 3 h the mixture was filtered in a dry-box under pure N_2 . The clear solution gave a negative test for halogen when a sample was hydrolysed and treated with silver nitrate. Usual titration showed between 0.12 and 0.2 mol dibenzylmagnesium.

Reaction of Benzylmagnesium Chloride with Formaldehyde.—To a solution containing benzylmagnesium chloride (0.008 75 mol) in diethyl ether (obtained as above) (35 ml) was added gaseous formaldehyde [from paraformaldehyde (3.8 g) (as described previously)] over 15 min. The mixture was stirred for 1 h at 0 °C then hydrolysed and worked up as usual to give a liquid (0.522 g). G.l.c. (3-phenylbutan-1-ol as internal standard) showed the presence of 2-phenylethanol (12) (0.023 g, 2.5%) and 0.0057 g (0.5%) of 2-methylbenzyl alcohol (13). Column chromatography of the crude product using acetone-chloroform (12:88 v/v) as eluant gave 2-(2-hydroxyethyl)benzyl alcohol (14) (0.271 g, 20.5%). Column chromatography which avoids any decomposition⁸ seems a better method for analysing diols than g.l.c.

Reaction of Dibenzylmagnesium with Formaldehyde.—To a solution containing dibenzylmagnesium (0.0061 mol) in diethyl ether (50 ml) was added gaseous formaldehyde [from paraformaldehyde (3.7 g)]. The mixture was stirred for 1 h at 0 °C then hydrolysed and worked up as usual to give a crude product (1.117 g), shown (g.l.c.) to contain (12) (0.0187 g, 1.3%) and (13) (0.294 g, 20%). Column chromatography as above gave only traces of the diol (14) (<1%).

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